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<b>(21) International Application Number:</b> PCT/US96/10439 <b>(22) International Filing Date:</b> 7 June 1996 (07.06.96)  <b>(30) Priority Data:</b> 60/000,105                      9 June 1995 (09.06.95)                      US  <b>(71) Applicant (for all designated States except US):</b> EURO-CELTIQUE, S.A. [LU/LU]; 122, boulevard de la Petrusse, L-2330 Luxembourg (LU).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CHASIN, Mark [US/US]; 3 Wayne Court, Manalapan, NJ 07726 (US). GOLDENHEIM, Paul [US/US]; 4 Bald Hill Place, Wilton, CT 06897 (US). SACKLER, Richard [US/US]; 25 Windrose Way, Greenwich, CT 06830 (US). TIGNER, Joseph [US/US]; 1 Santa Lane, New Milford, CT 06776 (US). BURCH, Ronald, Martin [US/US]; 12A Powder Horn Hill Road, Wilton, CT 06897 (US).  <b>(74) Agents:</b> DAVIDSON, Clifford, M. et al.; Steinberg, Raskin & Davidson, P.C., 1140 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> FORMULATIONS AND METHODS FOR PROVIDING PROLONGED LOCAL ANESTHESIA		
<b>(57) Abstract</b>  A formulation and methods for inducing sustained regional local anesthesia in a patient comprising a substrate comprising a local anesthetic and an effective amount of a biocompatible, biodegradable, controlled release material prolonging the release of the local anesthetic from the substrate to obtain a reversible local anesthesia when implanted or injected in a patient, and a pharmaceutically acceptable, i.e., non-toxic, non-glucocorticoid augmenting agent effective to prolong the duration of the local anesthesia for a time period longer than that obtainable from the substrate without the augmenting agent.		

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## FORMULATIONS AND METHODS FOR PROVIDING PROLONGED LOCAL ANESTHESIA

### BACKGROUND OF THE INVENTION

5 The present invention is related to biodegradable controlled release formulations for the administration of locally active drugs, in particular, local anesthetics and compositions and methods for augmenting the potency and duration of the same.

10 While compounds utilized as general anesthetics reduce pain by producing a loss of consciousness, local anesthetics act by producing a loss of sensation in the localized area of administration in the body. The mechanism by which local anesthetics induce their effect, while not having been determined definitively, is generally thought to be based upon the ability to interfere with the initiation and transmission of the nerve impulse. The duration of action of a local anesthetics is proportional to the time during which it is in actual contact with the nervous tissues. Consequently, procedures or formulations that maintain localization of the drug at the nerve greatly prolong anesthesia.

15 All local anesthetics are toxic, i.e., potentially toxic, and therefore it is of great importance that the choice of drug, concentration, rate and site of administration, as well as other factors, be considered in their use. On the other hand, a local anesthetic must remain at the site long enough to allow sufficient time for the localized pain to subside.

20 Different devices and formulations are known in the art for administration of local anesthetics. For example, U.S. Patent Nos. 4,725,442 and 4,622,219 (Haynes) are directed to microdroplets of methoxyflurane-containing microdroplets coated with a phospholipid prepared by sonication, which are suitable for intradermal or intravenous injection into a patient for inducing local anesthesia. Such microdroplets are said to cause long-term local anesthesia when injected intradermally, giving a duration of anesthesia considerably longer than the longest acting conventional local anesthetic (bupivacaine).

U.S. Patent No. 5,188,837 (Domb) relates to a microsuspension system containing lipospheres having a layer of a phospholipid imbedded on their surface. The core of the liposphere is a solid substance to be delivered, or the substance to be delivered is dispersed in an inert vehicle. The substance to be delivered can be, e.g., nonsteroidal anti-inflammatory compounds, local anesthetics, water insoluble chemotherapeutic agents and steroids.

Other formulations directed to injectable microcapsules, etc. are known. For example, U.S. Patent No. 5,061,492 related to prolonged release microcapsules of a water-soluble drug in a biodegradable polymer matrix which is composed of a copolymer of glycolic acid and a lactic acid. The microcapsules are prepared as an injectable preparation in a pharmaceutically acceptable vehicle. The particles of water soluble drug are retained in a drug-retaining substance dispersed in a matrix of the lactic/glycolic acid copolymer in a ratio of 100/1 to 50/50 and an average molecular weight of 5,000-200,000. The injectable preparation is made by preparing a water-in-oil emulsion of aqueous layer of drug and drug retaining substance and an oil layer of the polymer, thickening and then water-drying.

U.S. Patent No. 4,293,539 (Ludwig, et al.) is directed to controlled release formulations comprised of a microbial agent dispersed throughout a copolymer derived from lactic acid and glycolic acid. The copolymer is derived from 60-95% lactic acid and 40-5% glycolic acid by weight, and has a molecular weight of 6,000-35,000. An effective amount of the copolymeric formulation is administered by subcutaneous or intramuscular administration.

WO 94/05265 describes improved biodegradable controlled release systems consisting of a polymeric matrix incorporating a local anesthetic for the prolonged administration of the local anesthetic agent. The devices are selected on the basis of their degradation profiles: release of the topical anesthetic in a linear, controlled manner over the period of preferably two weeks and degradation in vivo with a half-life of less than six months, more preferably two weeks, to avoid localized inflammation. The disclosure states that an anti-inflammatory can be incorporated

into the polymer with the local anesthetic to reduce encapsulation for optimal access of drug to its site of action. The anti-inflammatories that are said to be useful include steroids such as dexamethasone, cortisone, prednisone, and others routinely administered orally or by injection.

5           Several non-glucocorticoids have been reported to prolong the action of local anesthetics. Epinephrine in immediate release form is art known to briefly prolong the action of immediate release local anesthetics by inducing vasoconstriction adjacent to the site of injection. However, the duration of prolongation provided by immediate release epinephrine is on the order of about an  
10           hour, at best, in a highly vascularized tissue. This strategy is also severely limited by the risk of gangrene due to prolonged impairment of blood flow to local tissues. Dextrans and alkalinizing agents have also been suggested as local anesthesia prolonging agents, but have heretofore been reported to be ineffective for this purpose (Bonica et al., 1990, "Regional Analgesia With Local Anesthetics" THE  
15           MANAGEMENT OF PAIN, Second Edition, Volume II, Published, Lea & Febiger, Chapter 94, pages 1890-1892).

          Colchicine has been shown to suppress injury-induced ectopic nerve discharge in a model system of chronic pain utilizing injured nerve (Wall et al. (Eds), 1995, Textbook of Pain, Third Edition, Publ., Churchill Livingston, pages  
20           94-98; Devol et al., 1991, A Group Report: Mechanisms of neuropathic pain following peripheral injury. In: Basbaume A I, et al (eds). TOWARDS A NEW PHARMACOTHERAPY OF PAIN, Dahlem Konferenzen, Wiley, Chichester pp 417-440; Devor et al., 1985, Pain, 22:127-137 at 128 and Devor, 1983, Pain, 16:73-86). It has been reported in one study that colchicine was given for the treatment of low-  
25           back pain, although oral colchicine has been shown to be ineffective for the same indication (Schnebel et al., 1988, Spine 13(3):354-7). However, it has not heretofore been known to use colchicine to prolong local anesthesia.

Thus, it has not previously been known to combine or otherwise administer both a controlled release local anesthetic and a non-glucocorticosteroid agent for augmenting the duration of local anesthesia.

### OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide a biodegradable controlled release dosage form for providing prolonged local anesthetic treatment of localized areas in humans and animals. More particularly, it is an object of the invention to provide a local anesthetic in a biocompatible, biodegradable controlled release form which provides a prolonged local anesthesia.

It is a further object of the present invention to provide a method for prolonging the effect of a local anesthetic agent at a desired site of treatment which is safe, effective, and which effectively controls post-operative pain.

It is a still further object to prolong the duration of the local anesthesia produced by administering an augmenting agent, before, during or after administration of a local anesthetic according to the invention, to a topical site or after infiltration, injection or implantation of the compositions according to the invention.

In accordance with the above-mentioned objects and others, the invention is related to biodegradable and/or bioerodable controlled release formulations for the administration of a local anesthetic agent capable of providing a prolonged effect *in vivo*, in combination with a pharmaceutically acceptable augmenting agent which is effective to prolong the duration of the local anesthetic effect for a time period greater than that possible by the use of the local anesthetic in controlled release form by itself (without the augmenting agent) and methods for the manufacture thereof are disclosed. The controlled release formulation can be formed into slabs, rods, pellets, microparticles, (e.g., microspheres, microcapsules), spheroids and pastes. Preferably, the formulation is in a form suitable for suspension in isotonic saline, physiological buffer or other solution acceptable for injection into a patient.

The invention further provides methods for inducing localized anesthesia by implanting, inserting or injecting a controlled release formulation, e.g., in the form of injectable microspheres loaded with a local anesthetic in sustained release form, into a site at or adjacent to a nerve or nerves innervating a body region to provide local anesthesia. Thus, the controlled release formulation according to the invention must be applied, injected, infiltrated or implanted at a site in a patient where the local anesthetic agent is to be released.

Further aspects of the invention are directed to a method of treating a patient in need of a surgical procedure, comprising placing a local anesthetic in controlled release form in proximity to a nerve or nerves at a site to be anesthetized, e.g., a surgical site, and previously, simultaneously and/or subsequently administering the aforementioned augmenting agent to substantially the same site to attain a prolongation of local anesthesia otherwise unattainable via the use of the local anesthetic alone.

The invention also provides for a unit dosage of the controlled release formulation comprising, in a container, a sufficient amount of the formulation to induce and/or prolong local anesthesia in at least one patient. In one embodiment, the unit dosages are sterile and lyophilized. Alternatively, the unit dosages are sterile and prepared as a suspension in a solution acceptable for injection into a patient.

The invention is further directed in part to novel formulations for providing local anesthesia, comprising a pharmaceutically-acceptable local anesthetic agent or a mixture of multiple different local anesthetic agents, in controlled release form, said formulation being capable of being placed in proximity to a nerve which is to be anesthetized, and an effective amount of a augmenting agent capable of prolonging the localized anesthetic effect provided by the local anesthetic in controlled release form. The augmenting agent may be incorporated with the local anesthetic in controlled release form, or alternatively, at least part of the dose of the augmenting agent may be administered separately but in proximity to the same



location as the local anesthetic. At least a part of such a separate dose may be administered later in time than the local anesthetic, to provide additional augmentation of the extent and/or duration of the local anesthetic effect. A portion of the local anesthetic can be administered to the desired site in immediate release form as long as a portion of the local anesthetic is also administered in controlled release form. On the other hand, the augmenting agent can be administered to substantially the same site at the same time as the local anesthetic, at a later time than the local anesthetic, or both, so long as the nerve blockade effect of the local anesthetic is substantially prolonged as compared to that which would be obtained with the local anesthetic alone.

In certain preferred embodiments of the invention, the local anesthetic is prepared in matrices of biodegradable controlled release injectable microspheres. Optionally, the augmenting agent is incorporated into these matrices along with the local anesthetic.

In further embodiments, the invention is directed to a suspension comprising a plurality of biocompatible, biodegradable controlled release microspheres comprising a local anesthetic agent, together with an augmenting agent which is incorporated in the controlled release microspheres, or dissolved or suspended in the suspension of microspheres. The suspension is, for example, suitable for administering the microspheres by injection.

In yet additional embodiments of the present invention, the local anesthetic is incorporated into a controlled release matrix having the augmenting agent coated on the surface thereof.

In yet additional embodiments of the invention, the formulation comprises a local anesthetic core; an augmenting agent present in the core in an amount effective to prolong the effect of the local anesthetic in an environment of use, and a biocompatible, biodegradable coating on the core providing a slow release of the local anesthetic and/or augmenting agent in an environment of use.

In further embodiments, a portion or all of the local anesthetic is incorporated onto an outer surface of the coated substrate and a portion or all of the augmenting agent is optionally incorporated in the core, so that, e.g., augmenting agent continues to be released after the local anesthetic has dispersed from the controlled release material.

Where the local anesthetic is applied topically to epidermal and/or mucosal surfaces, the augmenting agent may also be topically applied before, after or simultaneously with the local anesthetic.

The augmenting agent may be systemically administered by injection or infiltration, instillation, oral dosing or other method to obtain the desired prolongation of effect. Systemic administration, (e.g., oral or intravenous) while effective, will require a higher total dose of an augmentation agent than with local administration in proximity to the local anesthetic.

The controlled release local anesthetic dosage form may be injected or infiltrated, with or without an augmenting agent, at the site where the anesthetic is to be released. This can be prior to surgery, at the time of surgery, or following removal (discontinuation) or reversal of a systemic anesthetic.

In one preferred embodiment, the formulation is prepared in the form of microspheres. The microspheres may be prepared as a homogenous matrix of a local anesthetic with a biodegradable controlled release material, with the augmenting agent optionally incorporated therein. The microspheres are preferably prepared in sizes suitable for infiltration and/or injection, and injected at the site where the anesthetic is to be released before surgery, during the time of surgery, or following removal or reversal of systemic anesthetic.

Augmenting agents according to the present invention are pharmaceutically acceptable agents and include, for example, alkalinizing agents, non-glucocorticoid steroids such as neuroactive steroids, modulators of gamma amino butyric acid receptors, modulators of ionic transport across cell membranes, antipyretic agents, adrenergic receptor agonists or antagonists, tubulin binding agents, osmotic

polysaccharides, agonists and antagonists of potassium ATP channels, Na, K-ATPase inhibitors and enhancers, neurokinin antagonists, phosphatidylinositol-specific phospholipase C ("PLC") inhibitors, inhibitors of leukocyte glucose metabolism, anti-convulsants, analeptics, a tranquilizing agent, antidepressant, an  
5 convulsant, leukotriene and prostaglandin agonists and inhibitors, phosphodiesterase agonists and inhibitors, vasoconstrictive agents in sustained release form and combinations of any of the foregoing.

Examples demonstrate prolongation of the duration of local anesthesia with the greater prolongation being provided by the combination of a local anesthetic  
10 with a non-glucocorticoid augmenting agent.

#### **DETAILED DESCRIPTION**

Accordingly, the present invention provides for pharmaceutically acceptable augmenting agent or agents in conjunction with a local anesthetic in controlled  
15 release form that significantly increases the time period of local anesthesia when administered at a site in a patient. The augmentation of efficacy provided by the use of the augmenting agent cannot be predicted based on *in vitro* release (dissolution) of the local anesthetic in controlled release form: the inclusion of the augmenting agent within the controlled release formulations of the invention does not  
20 substantially alter or prolong the *in vitro* dissolution rate of the local anesthetic agent from the formulation; yet, the same formulation when administered *in vivo* provides a significant increase in the time period of local anesthesia at the site of administration. The augmenting agents disclosed herein are non-glucocorticoid agents and can be administered prior to, along with, or after administration, e.g.,  
25 application, infiltration and/or injection of the local anesthetic agent in controlled release form, in each case with a substantial prolongation of local anesthesia *in vivo*.

The augmenting agent can be compounded in the same controlled release formulation as a local anesthetic agent or agents, in a separate controlled release formulation, e.g., different injectable microspheres, or in a non-controlled release,

i.e, immediate release formulation. The augmenting agent may be administered before, simultaneously with, or after injection or infiltration, implantation or insertion of the controlled release local anesthetic formulation at the desired site.

In those embodiments of the invention directed to formulations where the augmenting agent is included in the formulation with the local anesthetic, the augmenting agent may be included in controlled release form or in immediate release form. The augmenting agent may be incorporated into any pharmaceutically acceptable carrier and preferably a carrier providing controlled release, including, e.g., a controlled release matrix along with the local anesthetic; incorporated into a controlled release coating on a controlled release device or formulation; or incorporated as an immediate release layer coating the local anesthetic formulation. On the other hand, the augmenting agent may be incorporated into a pharmaceutically acceptable aqueous medium suitable for infiltration or injection, either in controlled release form or in immediate release form.

#### Definitions

The controlled release formulations and methods of the invention may be used in conjunction with any system for application, infiltration, implantation, insertion, or injection known in the art, including but not limited to microparticles, e.g., microspheres or microcapsules, gels, pastes, implantable rods, pellets, plates or fibers, and the like (generically referred to as "substrates").

As used herein, the terms, "sustained release" and "controlled release" are well understood in the art and are intended to be interchangeable.

As used herein, the terms "local anesthetic agent" or "local anesthetic" means any drug which provides local numbness and/or analgesia. The term also includes, but is not limited to, any drug which, when locally administered, e.g., topically or by infiltration or injection, provides localized full or partial inhibition of sensory perception and/or motor function. Under either definition, the localized condition so induced is also referred to herein as "local anesthesia". Local

anesthetic agents which can be used include, simply by way of example, bupivacaine, ropivacaine, dibucaine, procaine, chloroprocaine, prilocaine, mepivacaine, etidocaine, tetracaine, lidocaine, and xylocaine, as well as anesthetically active derivatives, analogs and mixtures thereof. The local anesthetic can be in the form of a salt, for example, the hydrochloride, bromide, acetate, citrate, carbonate or sulfate. More preferably, the local anesthetic agent is in the form of a free base. The free base provides a slower initial release and avoids an early "dumping" of the local anesthetic at the injection site. Preferred local anesthetic agents include, e.g., bupivacaine. Local anesthetic agents typically administered systematically may also be used in those cases where the means of administration results only in a local effect, rather than systemic. The term "local anesthetic" may also encompass, pursuant to the definitions provided herein, a drug of a different class than those traditionally associated with local anesthetic properties, including but not limited to morphine, fentanyl, and agents which, for example, can provide regional blockade of nociceptive pathways (afferent and/or efferent).

As used herein, the term "patient" broadly refers to any animal that is to be treated with the compositions and by the methods herein disclosed. The disclosed local anesthetic dosage form can provide localized pain blockade to any animal, e.g., any vertebrate, which it is desired to so anesthetize. In particular, the disclosed methods and compositions will find use in veterinary practice and animal husbandry for, e.g., birds and mammals, wherever prolonged local anesthesia is convenient or desirable. In a preferred embodiment, the term includes humans in need of or desiring prolonged local anesthesia.

#### Augmenting Agents

Augmenting agents according to the invention are compositions or compounds that prolong the duration of local anesthesia and/or enhance the effectiveness of local anesthetic agents when delivered to the site of local anesthetic

administration before, simultaneously with or after the local anesthetic is administered. The augmenting agents are not glucocorticosteroid agents.

In one embodiment, the augmenting agents include an alkalinizing agent. The alkalinizing augmenting agents used herein preferably raise the pH of the medium in which the local anesthetic agents in controlled release form are present (e.g., either an injection medium or the environment at the site of injection) to provide a pH from about 6.0 to about 8.5, preferably from about 7.5 to about 8.5. Preferably, the alkalinizing agent may be, for example, a carbonate buffer such as sodium carbonate. Of course, any other alkalinizing agent that is pharmaceutically acceptable for localized injection or infiltration may also be effectively employed.

The augmenting agents also include non-glucocorticoid steroids such as e.g., androgens, such as testosterone and its active derivatives, analogs and metabolites; estrogens, such as estradiol and its active derivatives, analogs and metabolites and progestins, such as progesterone and its active derivatives, analogs and metabolites and mixtures of any of these.

In another embodiment, the augmenting agents are neuroactive steroids, such as, e.g., one or more of the class of anesthetic steroids. Neuroactive steroids useful as augmenting agents according to the invention also include those which modulate GABA receptors. Preferred neuroactive steroids include, simply by way of example, althesin and its main component, alphaxalone and active analogs, derivatives and mixtures thereof, as well as 5-alpha-pregnane-3 alpha-21-diol-20-one (tetrahydro-deoxycorticosterone or THDOC) and/or allotetrahydrocortisone (the 17-beta configuration); and dehydroepiandrosterone ("DHE") and active analogs, derivatives and mixtures thereof. Preferably, the neuroactive steroids are present as an additive in the vehicle carrying the microspheres in a concentration ranging from about 0.01 to about 1 percent by weight, and most preferably from about 0.05 to about 0.5 percent by weight.

The augmenting agents also include non-steroidal modulators of GABA receptors, including those that are capable of potentiating the inhibitory effects of

GABA on those receptors. Preferably, these include the benzodiazepenes, e.g., diazepam as well as its active derivatives, analogs and metabolites and mixtures thereof. More preferably, the diazepam is present as an additive in the vehicle in a concentration ranging from about 0.01 to about 1 percent by weight, and most preferably from about 0.05 to about 0.5 percent by weight. Of course, the artisan will appreciate that the potency of benzodiazepenes varies widely, and will adjust these concentration ranges accordingly for other benzodiazepenes, relative to the potency of diazepam.

In yet another aspect of the invention, the augmenting agent is a modulator of ionic transport across cell membranes. Monovalent and multivalent metal ion transport can be modulated. Agents include, e.g., sodium, potassium and calcium channel modulators (e.g., nifedipine, nitrendipine, verapamil, etc.). In preferred embodiments, these also include, but are not limited to, aminopyridine, benzamil, diazoxide, 5,5 diphenylhydantoin, minoxidil, tetraethylammonium and valproic acid. Preferably, the ion transport modulating agent is present as an additive in the vehicle carrying the microspheres in a concentration ranging from about 0.01 to about 5 percent by weight, and most preferably from about 0.05 to about 1.5 percent by weight.

Augmenting agents also include, e.g., antipyretic agents such as aminopyrine, phenazone, dipyrone, apazone, phenylbutazone and derivatives and analogs thereof. Aminopyrine is preferably included in the vehicle containing the microspheres in a concentration ranging from about 0.01 to about 0.5 percent and in a more preferred embodiment the concentration ranges from about 0.05 to about 0.5 percent, by weight.

Other preferred augmenting agents include, e.g., adrenergic receptor modulators, such as  $\alpha_2$  receptor agonists, can also be used as augmenting agents. Simply by way of example, the  $\alpha_2$  receptor agonist clonidine provides useful augmentation of local anesthesia, although any other art known  $\alpha_2$  receptor modulators capable of augmenting local anesthesia according to the invention may

be used. Clonidine is preferably included in the vehicle containing the microspheres in a concentration ranging from about 0.01 to about 0.5 percent and in a more preferred embodiment the concentration ranges from about 0.05 to about 1.0 percent, by weight.

5           Tubulin binding agents that are capable of promoting the formation or disruption of cytoplasmic microtubules are may be employed as augmenting agents according to the invention. Such agents include, for example, colchicine and the vinca alkaloids (vincristine and vinblastine) as well as active derivatives, analogs metabolites and mixtures thereof. Of course, some agents may be classified in more  
10           than one category, thus, for example, colchicine is also known to inhibit glucose metabolism in leukocytes. Colchicine is preferably included in the vehicle containing the microspheres in a concentration ranging from about 0.01 to about 1.0 percent and in a more preferred embodiment the concentration ranges from about 0.05 to about 0.5 percent, by weight.

15           Osmotic polysaccharides are also able to be used as augmenting agents. In a one preferred embodiment, the osmotic polysaccharide includes dextran. More preferably, the dextran augmenting agents according to the invention have a molecular weight ranging from 20 kDa through 200 kDa, or greater. A solution containing dextran in a form suitable for injection or infiltration into a desired site in  
20           a patient is preferably buffered to a pH ranging from 3.0 to 8.5, but in a preferred aspect is buffered to a pH ranging from 7.0 to 8.5.

          Other preferred embodiments of the invention provide for potassium-ATP channel agonists for use as augmenting agents. A preferred potassium-ATP channel agonist is, e.g., diazoxide, as well as its active derivatives, analogs, metabolites and  
25           mixtures thereof are useful as augmenting agents.

          Sodium/potassium ATPase inhibitors are also preferred as augmenting agents according to the invention. Preferably, the sodium/potassium ATPase inhibitors are cardiac glycosides that are effective to augment local anesthesia. Cardiac glycosides that are useful according to the invention include, e.g., ouabaine,



digoxin, digitoxin and active derivatives, analogs and metabolites and mixtures of any of these.

Additionally, augmenting agents according to the invention include, e.g., neurokinin antagonists, such as, e.g., spantide and other peptide inhibitors of substance P receptors that are well known to the art, e.g., as are listed in Receptor and Ion Channel Nomenclature Supplement, Trends in Pharmacological Sciences 18:64-65, the disclosure of which is incorporated by reference herein in its entirety. PLC inhibitors such as, e.g., 1-[6-[[17-beta-3-methoxyestra-1,3,5(10)-triene-17-yl]amino]hexyl]-1-H-pyrrole-2,5-dione, and anti-seizure agents and agents that stabilize cell membrane potential, such as, e.g., benzodiazepines, barbiturates, deoxybarbiturates, carbamazepine, succinamides, valproic acid, oxazolidienbiones, phenacemide and active derivatives, analogs and metabolites and mixtures thereof. Preferably, the anti-seizure augmenting agent is phenytoin, and most preferably is 5,5-diphenylhydantoin.

Surprisingly, locally acting vasoconstrictive agents, also provide effective augmentation of local anesthesia that is unexpectedly superior to that provided by immediate release vasoconstrictive agents. While not wishing to be bound by any hypothesis as to how vasoconstrictive agents in sustained release form might greatly prolong local anesthetic activity, it is believed that sustained release vasoconstrictor agents provide a controlled and non-toxic vasoconstrictor activity that reduces the rate of local anesthetic washout from the treated tissue area to prolong the presence of effective concentrations of local anesthetic in the tissue. It is known to the art that vasoconstrictors, e.g., epinephrine, prolong local anesthetic activity for, at best, about 1 hour and that if excessive amounts of epinephrine or other vasoconstrictor is administered in an attempt to further prolong local anesthesia, local circulation may be so disrupted as to cause tissue necrosis and gangrene.

Surprisingly, controlled release vasoconstrictor agents can achieve local tissue concentrations that are safe and effective to provide vasoconstrictor activity effective to substantially prolong local anesthesia. More surprisingly, the local

circulatory bed, i.e., blood vessels, remain responsive to the vasoconstrictor agent for prolonged periods, e.g., receptor desensitization or smooth muscle fatigue or tolerance does not prevent the prolongation effect. The gradual release from a sustained release formulation also serves to greatly reduce the risk of toxic reactions such as, e.g., localized tissue necroses

As for the previously discussed augmenting agents, vasoconstrictive augmenting agents can be administered before, simultaneously with or after the administration of local anesthetic. In one embodiment of the invention, at least a portion of the vasoconstrictive agent is formulated in a sustained release formulation together with local anesthetic. In another embodiment, the vasoconstrictive agent is prepared in one or separate sustained release formulations. It will be appreciated that by manipulating the loading of, e.g., microspheres containing vasoconstrictor agent, the artisan can determine the number of microspheres necessary to administer a given dose. Thus, simply by way of example, microspheres loaded with about 75 percent by weight of vasoconstrictor agent will require half of the microspheres necessary to administer a predetermined dose than will microspheres loaded with about 45 percent by weight of vasoconstrictor agent.

Vasoconstrictor agents can be formulated into, e.g., sustained release microspheres including both a local anesthetic, e.g., bupivacaine free base, and a vasoconstrictor agent. Vasoconstrictor agents can also be formulated into, e.g., sustained release microspheres including local anesthetic without a vasoconstrictive agent.

In one embodiment, local anesthetic and vasoconstrictor agents are administered simultaneously in the form of, e.g., separate microspheres suspended in a single medium suitable for injection or infiltration, or in separate microspheres suitable for injection, e.g., at the same site. In a further embodiment, simply by way of example, administration of sustained release microspheres with combined local anesthetic and vasoconstrictor agent can also be followed by one or more additional

administrations of such combination formulation and/or of microspheres including as the active agent only local anesthetic or only vasoconstrictor agent.

Augmenting agents that are vasoconstrictor agents in sustained release form include, but are not limited to, catecholamines e.g., epinephrine, norepinephrine and dopamine as well as, e.g., metaraminol, phenylephrine, methoxamine, mephentermine, methysergide, ergotamine, ergotamine, dihydroergotamine, sumatriptan and analogs, and alpha-1 and alpha-2 adrenergic agonists, such as, e.g., clonidine, guanfacine, guanabenz and dopa (i.e., dihydroxyphenylalanine), methyl dopa, ephedrine, amphetamine, methamphetamine, methylphenidate, ethyl norepinephrine, ritalin, pemoline and other sympathomimetic agents, including active metabolites, derivatives and mixtures of any of the foregoing.

In a more preferred embodiment, at least a portion of any of the augmenting agents enumerated above are included in the controlled release formulation, in combination with a local anesthetic agent or agents in a concentration ranging from about 0.01 to about 30 percent or more, by weight, relative to the weight of the formulation.

The artisan will also appreciate that other augmenting agents according to the invention broadly include any other types and classifications of drugs or active agents known to the art. Such augmenting agents are readily identified by routine screening as discussed hereinbelow using animal sensory and motor quantitation protocols well known to the art.

A local anesthetic according to the invention can also be formulated, e.g., in injectable microspheres, in combination with at least one vasoconstrictor augmenting agent according to the invention. In one embodiment, the vasoconstrictor can be included in the vehicle suitable for injection carrying the microspheres. In a further embodiment, at least a portion of the vasoconstrictor can also be formulated into a sustained release formulation, e.g., injectable microspheres, together with the local anesthetic. In a still further embodiment, at

least a portion of the vasoconstrictor can be prepared in a separate sustained release formulation.

The vasoconstrictor can be included in either a single or combination formulation in an amount ranging from about 0.001 percent to about 90 percent, by weight relative to the total weight of the formulation. Preferably, the vasoconstrictor is included in a controlled release formulation in an amount ranging from about 0.005 percent to about 20%, and more preferably, from about 0.05 percent to about 5 percent, by weight, relative to the total weight of the formulation. When a vasoconstrictor is present in the injection vehicle in immediate release form, it is present in amounts ranging from about 0.01% to about 5 percent, or more, by weight, relative to the injection vehicle. The vasoconstrictor can also be provided in a ratio of local anesthetic, e.g., bupivacaine to vasoconstrictor, ranging from about 10:1 to about 20,000 and preferably from about 100:1 to about 2000:1 and from about 500:1 to about 1500:1.

Of course, the artisan will appreciate that the amounts of augmenting agent and local anesthetic will vary depending upon the relative potency of the agents selected, the depth and duration of local anesthesia desired.

Of course, the artisan will appreciate that the optimal concentration and/or quantities or amounts of any particular augmenting agent, whether present in the injection vehicle, separately administered before, during or after local anesthesia is induced or whether included in the microsphere formulation, may be adjusted to accommodate variations in the treatment parameters. Such treatment parameters include the polymer composition of a particular microsphere preparation, the particular local anesthetic utilized, and the clinical use to which the preparation is put, in terms of the site treated for local anesthesia, the type of patient, e.g., human or non-human, adult or child, and the type of sensory stimulus to be anesthetized.

Further, the concentration and/or amount of any particular augmenting agent for a given formulation may readily identified by routine screening in animals, e.g, rats, by screening a range of concentration and/or amounts of augmenting agent

using the hotplate foot withdrawal assay and/or motor function assay described hereinbelow. Art known methods are also available to assay local tissue concentrations, diffusion rates from microspheres and local blood flow before and after administration of local anesthetic formulations according to the invention.

5 One such method is microdialysis, as reviewed by T.E. Robinson et al., 1991, MICRODIALYSIS IN THE NEUROSCIENCES, Techniques, volume 7, Chapter 1, pages 1-64. The methods reviewed by Robinson can be applied, in brief, as follows. A microdialysis loop is placed in situ in a test animal. Dialysis fluid is pumped through the loop. When microspheres according to the invention are  
10 injected adjacent to the loop, released drugs, e.g., bupivacaine and vasoconstrictor augmenting agents, are collected in the dialysate in proportion to their local tissue concentrations. The progress of diffusion of the active agents can be determined thereby with suitable calibration procedures using known concentrations of active agents. For the vasoconstrictor augmenting agents, decrements and durations of  
15 vasoconstriction effects can be measured by clearance rates of marker substances, e.g., methylene blue or radiolabeled albumen from the local tissue. from the microspheres, as well as the local blood flow

The optimal concentration of augmenting agent for human clinical use may also be readily determined by routine animal screening as described hereinbelow,  
20 and further adjusted, where indicated, by routine clinical experience.

#### Formulations

Any pharmaceutically acceptable carrier vehicle or formulation suitable for local implantation, infiltration or injection in proximity to a nerve that is able to  
25 provide a controlled release of a local anesthetic agent and/or augmenting agent may be employed to provide for prolonged local anesthesia as needed. Slow release formulations known in the art include specially coated pellets, polymer formulations or matrices for surgical insertion or as controlled release microparticles, e.g., microspheres or microcapsules, for implantation, insertion or injection, wherein the

slow release of the active medicament is brought about through controlled diffusion out of the matrix and/or selective breakdown of the coating of the preparation or selective breakdown of a polymer matrix. Other formulations or vehicles for controlled or immediate delivery of an agent to a preferred localized site in a patient include, e.g., suspensions, emulsions, liposomes and any other suitable, art known, delivery vehicle or formulation.

In a preferred embodiment, the slow release formulation is prepared as microspheres in a size distribution range suitable for local infiltration or injection. The diameter and shape of the microspheres or other particles can be manipulated to modify the release characteristics. For example, larger diameter microspheres will typically provide slower rates of release and reduced tissue penetration and smaller diameters of microspheres will produce the opposite effects, relative to microspheres of different mean diameter but of the same composition. In addition, other particle shapes, such as, for example, cylindrical shapes, can also modify release rates by virtue of the increased ratio of surface area to mass inherent to such alternative geometrical shapes, relative to a spherical shape. The diameter of injectable microspheres are in a size range from, for example, from about 5 microns to about 200 microns in diameter. In a more preferred embodiment, the microspheres range in diameter from about 20 to about 120 microns.

A wide variety of biodegradable materials may be utilized to provide the controlled release of the local anesthetic. Any pharmaceutically acceptable biodegradable polymers known to those skilled in the art may be utilized. It is preferred that the biodegradable controlled release material degrade *in vivo* over a period of less than about two years, with at least 50% of the controlled release material degrading within about one year, and more preferably six months or less. More preferably, the controlled release material will degrade significantly within one to three months, with at least 50% of the material degrading into non-toxic residues which are removed by the body, and 100% of the drug being released within a time period from about two weeks to about two months. The controlled release material

should preferably degrade by hydrolysis, and most preferably by surface erosion, rather than by bulk erosion, so that release is not only sustained but also provides desirable release rates. However, the pharmacokinetic release profile of these formulations may be first order, zero order, bi- or multi-phasic, to provide the desired reversible local anesthetic effect over the desired time period.

The controlled release material should be biocompatible. In the case of polymeric materials, biocompatibility is enhanced by recrystallization of either the monomers forming the polymer and/or the polymer using standard techniques.

Suitable biodegradable polymers can be utilized as the controlled release material. The polymeric material may comprise a polylactide, a polyglycolide, a poly(lactide-co-glycolide), a polyanhydride, a polyorthoester, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, soluble derivatives of polysaccharides, soluble derivatives of proteinaceous polymers, polypeptides, polyesters, and polyorthoesters or mixtures or blends of any of these. The polysaccharides may be poly-1,4-glucans, e.g., starch glycogen, amylose, amylopectin, and mixtures thereof. The biodegradable hydrophilic or hydrophobic polymer may be a water-soluble derivative of a poly-1,4-glucan, including hydrolyzed amylopectin, hydroxyalkyl derivatives of hydrolyzed amylopectin such as hydroxyethyl starch (HES), hydroxyethyl amylose, dialdehyde starch, and the like. Preferred controlled release materials which are useful in the formulations of the invention include the polyanhydrides, co-polymers of lactic acid and glycolic acid wherein the weight ratio of lactic acid to glycolic acid is no more than 4:1 (i.e., 80% or less lactic acid to 20% or more glycolic acid by weight), and polyorthoesters containing a catalyst or degradation enhancing compound, for example, containing at least 1% by weight anhydride catalyst such as maleic anhydride. Other useful polymers include protein polymers such as gelatin and fibrin and polysaccharides such as hyaluronic acid. Since polylactic acid takes at least one year to degrade *in vivo*, this polymer should be utilized by itself only in circumstances where such a degradation rate is desirable or acceptable.

The polymeric material may be prepared by any method known to those skilled in the art. For example, where the polymeric material is comprised of a copolymer of lactic and glycolic acid, this copolymer may be prepared by the procedure set forth in U.S. Patent No. 4,293,539 (Ludwig, et al.), the disclosure of which is hereby incorporated by reference in its entirety. In brief, Ludwig prepares such copolymers by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). The amount of catalyst is not critical to the polymerization, but typically is from about 0.01 to about 20 parts by weight relative to the total weight of combined lactic acid and glycolic acid. The polymerization reaction may be conducted without solvents at a temperature from about 100° C to about 250° C for about 48 to about 96 hours, preferably under a reduced pressure to facilitate removal of water and by-products. The copolymer is then recovered by filtering the molten reaction mixture to remove substantially all of the catalyst, or by cooling and then dissolving the reaction mixture in an organic solvent such as dichloromethane or acetone and then filtering to remove the catalyst.

Pharmaceutically acceptable polyanhydrides which are useful in the present invention have a water-labile anhydride linkage. The rate of drug release can be controlled by the particular polyanhydride polymer utilized and its molecular weight. The polyanhydride polymer may be branched or linear. Examples of polymers which are useful in the present invention include homopolymers and copolymers of poly(lactic acid) and/or poly(glycolic acid), poly[bis(p-carboxyphenoxy)propane anhydride] (PCPP), poly[bis(p-carboxy)methane anhydride] (PCPM), polyanhydrides of oligomerized unsaturated aliphatic acids, polyanhydride polymers prepared from amino acids which are modified to include an additional carboxylic acid, aromatic polyanhydride compositions, and copolymers of polyanhydrides with other substances, such as fatty acid terminated polyanhydrides, e.g., polyanhydrides polymerized from monomers of dimers and/or trimers of unsaturated fatty acids or unsaturated aliphatic acids. Polyanhydrides



may be prepared in accordance with the methods set forth in U.S. Patent No. 4,757,128, hereby incorporated by reference. For example, polyanhydrides may be synthesized by melt polycondensation of highly pure dicarboxylic acid monomers converted to the mixed anhydride by reflux in acetic anhydride, isolation and purification of the isolated prepolymers by recrystallization, and melt polymerization under low pressure ( $10^{-4}$  mm) with a dry ice/acetone trap at a temperature between 140°-250° C. for 10-300 minutes. High molecular weight polyanhydrides are obtained by inclusion of a catalyst which increases the rate of anhydride interchain exchange, for example, alkaline earth metal oxides such as CaO, BaO and CaCO<sub>3</sub>. Polyorthoester polymers may be prepared, e.g., as set forth in U.S. Patent No. 4,070,347, hereby incorporated by reference.

Proteinaceous polymers may also be used. Proteinaceous polymers and their soluble derivatives include gelation biodegradable synthetic polypeptides, elastin, alkylated collagen, alkylated elastin, and the like. Biodegradable synthetic polypeptides include poly-(N-hydroxyalkyl)-L-asparagine, poly-(N-hydroxyalkyl)-L-glutamine, copolymers of N-hydroxyalkyl-L-asparagine and N-hydroxyalkyl-L-glutamine with other amino acids. Suggested amino acids include L-alanine, L-lysine, L-phenylalanine, L-valine, L-tyrosine, and the like.

In embodiments where the biodegradable polymer comprises a gel, one such useful polymer is a thermally gelling polymer, e.g., polyethylene oxide, polypropylene oxide (PEO-PPO) block copolymer such as Pluronic® F127 from BASF Wyandotte. In such cases, the local anesthetic formulation may be injected via syringe as a free-flowing liquid, which gels rapidly above 30°C (e.g., when injected into a patient). The gel system then releases a steady dose of local anesthetic at the site of administration.

In additional embodiments, the controlled release material, which in effect acts as a carrier for the local anesthetic and/or the augmenting agent, can further include a bioadhesive polymer such as pectins (polygalacturonic acid),

mucopolysaccharides (hyaluronic acid, mucin) or non-toxic lectins or the polymer itself may be bioadhesive, e.g., polyanhydride or polysaccharides such as chitosan.

Definitions or further descriptions of any of the foregoing terminology are well known in the art and may be found by referring to any standard biochemistry reference text such as "Biochemistry" by Albert L. Lehninger, Worth Publishers, Inc. and "Biochemistry" by Lubert Stryer, W.H. Freeman and Company, both of which are hereby incorporated by reference.

The aforementioned biodegradable hydrophobic and hydrophilic polymers are particularly suited for the methods and compositions of the present invention by reason of their characteristically low human toxicity and virtually complete biodegradability.

The substrates of the presently described formulations in certain preferred embodiments are manufactured using a method that evenly disperses the local anesthetic throughout the formulation, such as emulsion preparation, solvent casting, spray drying or hot melt, rather than a method such as compression molding. A desired release profile can be achieved by using a mixture of polymers having different release rates and/or different percent loading of local anesthetic and/or augmenting agent, for example, polymers releasing in one day, three days, and one week. In addition, a mixture of microspheres having one or more different local anesthetic agents, having the same or different controlled release profile, can be utilized to provide the benefits of different potencies and spectrum of activity during the course of treatment.

Methods for manufacture of microspheres are well known and are typified in the following examples. Examples of suitable methods of making microspheres include solvent evaporation, phase separation and fluidized bed coating.

In solvent evaporation procedures, the local anesthetic agent, if soluble in organic solvents, may be entrapped in the biodegradable polymer by dissolving the polymer in a volatile organic solvent, adding the drug to the organic phase, emulsifying the organic phase in water which contains less than 2% polyvinyl

alcohol, and finally removing the solvent under vacuum to form discrete, hardened monolithic microspheres.

Phase separation microencapsulation procedures are suitable for entrapping water-soluble agents in the polymer to prepare microcapsules and microspheres.

5 Phase separation involves coacervation of the polymer from an organic solvent by addition of a nonsolvent such as silicone oil. In a preferred embodiment, the microspheres may be prepared by the process of Ramstack et al., 1995, in published international patent application WO 95/13799, the disclosure of which is incorporated herein in its entirety. The Ramstack et al. process essentially provides  
10 for a first phase, including an active agent and a polymer, and a second phase, that are pumped through a static mixer into a quench liquid to form microparticles containing the active agent. The first and second phases can optionally be substantially immiscible and the second phase is preferably free from solvents for the polymer and the active agent and includes an aqueous solution of an emulsifier.

15 In fluidized bed coating, the drug is dissolved in an organic solvent along with the polymer. The solution is then processed, e.g., through a Wurster air suspension coating apparatus to form the final microcapsule product.

The biodegradable controlled release materials may be used in order to prepare controlled release local anesthetic implants. The implants may be  
20 manufactured, e.g., by compression molding, injection molding, and screw extrusion, whereby the local anesthetic agent is loaded into the polymer. Implantable fibers can be manufactured, e.g., by blending the local anesthetic agent with the controlled release material and then extruding the mixture, e.g., under pressure, to thereby obtain biodegradable fibers. In certain preferred embodiments,  
25 the augmenting agent may be incorporated into the implant, or may be coated onto a surface of the implant.

In other embodiments of the invention, the controlled release material comprises an artificial lipid vesicle, or liposome. The use of liposomes as drug delivery systems is known, and comprehensive review articles on their properties

and clinical applications are available; see, e.g., Barenholz and Amselem, in  
"Liposome Technology", 2nd ed., G. Gregoriadis, ed., CRC Press, 1992;  
Lichtenberg and Barenholz, in Methods for Biochemical Analysis, 33, D. Glick, ed.,  
1988. A liposome is defined as a structure consisting of one or more concentric  
5 lipid bilayers separated by water or aqueous buffer compartments. These hollow  
structures, which have an internal aqueous compartment, can be prepared with  
diameters ranging from 20 nm to 10  $\mu$ m. They are classified according to their final  
size and preparation method as: SUV, small unilamellar vesicles (0.5-50 nm); LUV,  
large unilamellar vesicles (100 nm); REV, reverse phase evaporation vesicles (0.5  
10  $\mu$ m); and MLV, large multilamellar vesicles (2-10  $\mu$ m).

Liposomes as described herein will vary in size. Preferably, the liposomes  
have a diameter between 100 nm and 10 microns or greater. A wide variety of lipid  
materials may be used to form the liposomes including natural lecithins, e.g., those  
derived from egg and soya bean, and synthetic lecithins, the proviso being that it is  
15 preferred that the lipids are non-immunogenic and bio-degradable. Also, lipid-  
based materials formed in combination with polymers may be used, such as those  
described in U.S. Patent No. 5,188,837 to Domb, (incorporated by reference  
herein).

Examples of synthetic lecithins which may be used together with their  
20 respective phase transition temperatures, are di-(tetradecanoyl)phosphatidylcholine  
(DTPC) (23° C), di-(hexadecanoyl)phosphatidylcholine (DHPC) (41° C) and di-  
(octadecanoyl) phosphatidylcholine (DOPC) (55° C). Di-(hexadecanoyl)  
phosphatidylcholine is preferred as the sole or major lecithin, optionally together  
with a minor proportion of the di-(octadecanoyl) or the di-(tetradecanoyl)  
25 compound. Other synthetic lecithins which may be used are unsaturated synthetic  
lecithins, for example, di-(oleyl)phosphatidyl-choline and di-  
(linoleyl)phosphatidylcholine. In addition to the main liposome-forming lipid or  
lipids, which are usually phospholipids, other lipids (e.g. in a proportion of 5-40%  
w/w of the total lipids) may be included, for example, cholesterol or cholesterol

stearate, to modify the structure of the liposome membrane, rendering it more fluid or more rigid depending on the nature of the main liposome-forming lipid or lipids.

In certain embodiments, the augmenting agent is incorporated along with the local anesthetic agent into the lipid. In other preferred formulations, the lipids containing the local anesthetic agent are dispersed in a pharmaceutically acceptable aqueous medium. The augmenting agent may be incorporated into this aqueous medium. In a further embodiment, a portion of the dose of the local anesthetic is incorporated into the aqueous medium in immediate release form. The resultant formulation is an aqueous suspension which may comprise the local anesthetic and/or augmenting agent partitioned between a free aqueous phase and a liposome phase.

As an even further alternate embodiment, liposomes containing local anesthetic may be combined in an aqueous phase where liposomes containing the augmenting agent to form an aqueous pharmaceutical suspension useful for administration at the desired site in the patient to be anesthetized. This may be accomplished via injection or implantation. Liposomes may be prepared by dissolving an appropriate amount of a phospholipid or mixture of phospholipids together with any other desired lipid soluble components (e.g., cholesterol, cholesterol stearate) flowing in a suitable solvent (e.g., ethanol) and evaporating to dryness. An aqueous solution of the local anesthetic, optionally with augmenting agent, may then be added and mixed until a lipid film is dispersed. The resulting suspension will contain liposomes ranging in size, which may then be fractionated to remove undesirable sizes, if necessary. This fractionation may be effected by column gel chromatography, centrifugation, ultracentrifugation or by dialysis, as well known in the art.

The above method of preparation of liposomes is representative of a possible procedure only. Those skilled in the art will appreciate that there are many different methods of preparing liposomes, all of which are deemed to be encompassed by the present disclosure.

In additional embodiments of the invention, the substrate comprises a plurality of microcapsules laden with the local anesthetic agent with or without the augmenting agent. Microcapsules may be prepared, for example, by dissolving or dispersing the local anesthetic agent in an organic solvent and dissolving a wall forming material (polystyrene, alkylcelluloses, polyesters, polysaccharides, polycarbonates, poly(meth)acrylic acid ester, cellulose acetate, hydroxypropylmethylcellulose phthalate, dibutylaminohydroxypropyl ether, polyvinyl butyral, polyvinyl formal, polyvinylacetal-diethylamino acetate, 2-methyl-5-vinyl pyridine methacrylate-methacrylic acid copolymer, polypropylene, vinylchloride-vinylacetate copolymer, glycerol distearate, etc.) in the solvent; then dispersing the solvent containing the local anesthetic agent and wall forming material in a continuous-phase processing medium, and then evaporating a portion of the solvent to obtain microcapsules containing the local anesthetic agent in suspension, and finally, extracting the remainder of the solvent from the microcapsules. This procedure is described in more detail in U.S. Patent Nos. 4,389,330 and 4,530,840, hereby incorporated by reference.

The controlled release dosage forms of the present invention preferably provide a sustained action in the localized area to be treated. For example, it would be desirable that such a formulation provides localized anesthesia to the site for a period of one day, two days, three days, or longer. The formulations can therefore, of course, be modified in order to obtain such a desired result.

Microspheres and other injectable substrates described herein may be incorporating an effective amount of the same into a pharmaceutically acceptable solution (e.g., water) or suspension for injection. The final reconstituted product viscosity may be in a range suitable for the route of administration. In certain instances, the final reconstituted product viscosity may be, e.g., about 35 cps. Administration may be via the subcutaneous or intramuscular route. However, alternative routes are also contemplated, and the formulations may be applied to the localized site in any manner known to those skilled in the art, such that a localized

effect is obtained. The substrate formulations of the invention can be implanted at the site to be treated. Thereby, the formulations of the present invention, when including a local anesthetic, may be used in the control of post-operative pain.

5 The local anesthetic is incorporated into the polymer or other controlled-release formulation in a percent loading between 0.1% and 90% or more, by weight, preferably between 5% and 80%, or more, by weight and more preferably between 65 and 80%, or more, by weight. In an even more preferred embodiment, the local anesthetic is loaded at about 75% by weight.

10 It is possible to tailor a system to deliver a specified loading and subsequent maintenance dose by manipulating the percent drug incorporated in the polymer and the shape of the matrix or formulation, in addition to the form of local anesthetic (e.g., free base versus salt) and the method of production. The amount of drug released per day increases proportionately with the percentage of drug incorporated into the formulation, e.g., matrix (for example, from 5 to 10 to 20%). In the  
15 preferred embodiment, polymer matrices or other formulations with about 75% drug incorporated are utilized, although it is possible to incorporate substantially more drug, depending on the drug, the method used for making and loading the device, and the polymer.

20 When the augmenting agent is included in the controlled release substrates comprising local anesthetic, it has been found that useful loadings of augmenting agent are from about 0.001% to about 30% by weight of the substrate or preferably from about 0.01% to about 5% by weight of the substrate. When the augmenting agent is included in controlled release substrates without local anesthetic, it has  
25 been found that useful loadings of augmenting agent are from about 0.001 percent to about 90%, or more, by weight of the substrate, or preferably from about 0.001 to about 30% by weight of the substrate or more preferably from about 0.01% to about 5% by weight of the substrate.

When the augmenting agent is included as part of the (aqueous) injection medium, the augmenting agent may be present in a weight percent relative to the local anesthetic varying from about 0.01% to about 15%.

5 The dosage of the controlled release microsphere formulations is dependent upon the kind and amount of the drug to be administered, the recipient animal, and the objectives of the treatment. For example, when the local anesthetic included in the microspheres of the present invention is bupivacaine, the formulation may include, e.g., from about 0.5 to about 2 mg/kg body weight. The effective dose of bupivacaine, or an amount of another local anesthetic sufficient to provide  
10 proportional potency, can range from about 1 to 50 mg of bupivacaine injected or inserted at each site where the release of a local anesthetic agent is desired. In certain preferred embodiments, the dose of bupivacaine in the controlled release dosage form of the invention is sufficient to provide a controlled release of about 1 to 4 mg per day at the release site for at least 1 to 4 days. Since the formulations of  
15 the present invention are controlled release, it is contemplated that formulations may include much more than usual immediate release doses, e.g., as much as 120 mg/kg bupivacaine or more.

In certain preferred embodiments, the controlled release substrate comprising local anesthetic and/or augmenting agent provides from about 10 to  
20 about 60 percent release of drug, e.g., local anesthetic after 24 hours, from about 20 to about 80 percent release after 48 hours and from about 40 to about 100 percent release after 72 hours. More preferably, the controlled release substrate comprising local anesthetic provides from about 25 to about 40 percent release of local anesthetic after 24 hours, from about 40 to about 50 percent release after 24  
25 hours and from about 45 to about 55 percent release after 72 hours and 80 to 100 percent cumulative release is provided after about 280 hours.

In order to obtain a local anesthetic effect *in vivo* when combined with the augmenting agent as described herein of at least about 40 hours the augmenting agent is placed into approximately the same site in a patient (e.g., human or



veterinary) before, simultaneously with, or after the placement of a local anesthetic at that site. The presence of augmenting agent in the controlled release formulation does not significantly affect the *in vitro* release rates of local anesthetic.

5 In a preferred embodiment the local anesthetic effect is prolonged by the use of an augmenting agent by at least about 15%, e.g., from about 15% to about 1400% or more preferably from about 300% to about 1000 percent or more and more preferably from about 300% to about 500%, or more of the duration of the local anesthetic effect that is obtained from the same formulation without benefit of an augmenting agent. The duration of the local anesthetic effect prolonged by an  
10 augmenting agent ranges from about 30 minutes to about 150 hours, or more, and preferably from 1 hour to about 1 to about 24 hours or more, and more preferably from about 1 hour to about 12 hours, or more.

The rate of release of local anesthetic agent or other drugs incorporated into the formulation will also depend on the solubility properties of the local anesthetic  
15 or drug. The greater the solubility in water, the more rapid the rate of release in tissue, all other parameters being unchanged. For example, those local anesthetic agents having pH dependent solubility will be released more rapidly at the optimum pH for those compounds. Thus, the formulation may be optimized for the desired local anesthetic release rate by selecting local anesthetic agents having a desired  
20 water solubility in tissue, e.g., at tissue pH. Thus, a local anesthetic agent that is more soluble at acid pH will have a faster release rate in a relatively acidic (e.g., pH less than about 7.2) tissue. For example, in one embodiment, the formulation will have released, *in vitro*, at least 70 percent of a local anesthetic at 48 hours at about pH 6 and will have released at least 40 percent of a local anesthetic at a pH ranging  
25 from about 7.4 to about 8, at 48 hours. Other combinations are pH independent in their release.

The examples demonstrate that the above-described augmenting agents prolong the duration of local anesthesia *in vivo* and do not significantly alter the time course of release of bupivacaine *in vitro*.

### Applications

Potential applications include any condition for which localized nerve blockade is desirable. This includes both local anesthesia for the relief of pain and motor symptoms as well as local anesthesia for other medical purposes. The formulations and methods according to the invention can be used to provide two to five day intercostal blockade for thoracotomy, or longer term intercostal blockade for thoracic post-therapeutic neuralgia, lumbar sympathetic blockade for reflex sympathetic dystrophy, or three-day ilioinguinal/iliohypogastric blockade for hernia repair. Other potential applications include obstetrical or gynecological procedures. Yet further potential applications include providing localized temporary sympathectomy, e.g., blockade of sympathetic or parasympathetic ganglia to treat a variety of autonomic diseases, including circulatory dysfunction or cardiac dysrhythmias. The formulations may also be used to treat trigeminal neuralgia and other diseases of the cranial nerves as well as to provide a temporary nerve block to treat localized muscle spasm and treatment of retrobulbar conditions, e.g., eye pain. Other uses include intra-operative administration in order to reduce pain during and after the operative procedure, especially for plastic surgery procedures where prolonged local anesthesia will enhance the outcome. These systems can also be used for the management of various forms of persistent pain, such as postoperative pain, sympathetically maintained pain, or certain forms of chronic pain such as the pain associated with many types of cancer. These systems may also be used for blockade of nociceptive pathways (afferent and efferent) in patients with acute pancreatitis, ileus, or other visceral disorders. These are merely examples, and additional uses for both human and veterinary practice are immediately apparent to the artisan.

### Methods of Administration

In a preferred method of administration a dosage form, e.g., microspheres, are administered by injection into a site where local anesthetic agent is to be

released. Microspheres may be injected through a syringe or a trochar. Pellets or slabs may be surgically placed into a site where release of oral anesthetic agent is desired. Controlled release gels, pastes or suspensions, including gels, pastes or suspension containing microspheres, may also be administered topically to a skin or mucosal surface of the body to obtain topical, localized anesthesia.

As described below, microspheres according to the invention can be administered alone or in combination with a solution including a non-glucocorticosteroid augmenting agent in an amount effective to prolong the duration of local anesthesia. Alternatively, the microspheres include an amount of a non-glucocorticosteroid augment agent effective to prolong the duration of local anesthesia.

In another alternative, one or more augmenting agents can be administered before, simultaneously with or after administration of the controlled release local anesthetic, wherein the augmenting agent is formulated into a separate microsphere formulation for controlled release. The controlled release rate for the augmenting agents may be the same as or different than the controlled release rate for the local anesthetic. The separate microsphere can be administered in a single injection, i.e., in a single injection vehicle, or in separate injections simultaneously or at different times. In a further embodiment, it has been found that additional dose of augmenting agent may also be administered as an injectable solution, in an injectable carrier or in a controlled release carrier to the nerve to be blockaded after the controlled release local anesthesia has worn off, in order to reactivate the initial local anesthesia without the co-administration of additional local anesthetic.

The microspheres may be prepared from PLGA polymers ranging from, for example, PLGA in a ratio of 50/50, 65/35 or 75/25. An optimum composition has been determined to be PLGA 65/35. The microspheres, formulated with, e.g., PLGA 65/35 microspheres are administered in a dose ranging from, for example, 2 through 450 mg of microspheres 75% (w/w) loaded with a local anesthetic such as bupivacaine, per kg of the patient to be treated. In a preferred embodiment the

dose ranges from 5 through 450 mg/kg. In a more preferred embodiment the dose ranges from about 10 to about 150 mg/kg with PLGA 65/35. Certainly, the artisan will appreciate the fact that the dose ranges mentioned above are based on the potency of bupivacaine, and that exact effective dosages will vary with the particular relative potency and pharmacokinetics of each local anesthetic and will be able to readily adjust the dose according to the degree of blockade experienced by the patient.

The use of the above-described augmenting agents before, simultaneously with or after administration of a controlled release local anesthesia, results in prolonged anesthesia.

The formulation described herein can also be used to administer local anesthetic agents that produce modality-specific blockade, as reported by Schneider, et al., *Anesthesiology*, 74:270-281 (1991), or that possess physical-chemical attributes that make them more useful for sustained release than for single injection blockade, as reported by Masters, et al., *Soc. Neurosci. Abstr.*, 18:200 (1992), the teachings of which are incorporated herein.

#### **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

The following non-limiting examples illustrate the preparation of the formulations according to the invention and the effects of local anesthetic and augmenting agents alone and in combination.

#### **EXAMPLES 1-3 (SOLVENT EXTRACTION PROCESS)**

In Examples 1-3, bupivacaine microspheres are prepared by dissolving the bupivacaine base and the polymer in ethyl acetate. The polymer is 50:50 poly (D,L) lactic co-glycolic acid which has a mole percent composition of 50% lactide and 50% glycolide. This dispersed phase is then added to a solution of polyvinyl alcohol (PVA) in water (the continuous phase) with stirring. The resulting emulsion is monitored for droplet size, which is in turn controlled by the rate of

stirring. The emulsion is then added to water to extract the solvent and to harden the microspheres. The mixture is then filtered and the microspheres are dried under vacuum at room temperature. The desired particle size fraction is then collected by sieving.

Each of Examples 1-3 are prepared such that the microspheres have a relatively high drug content. In Example 1, the theoretical drug content is about 60%, and the size of the microspheres range from about 45 to about 90 microns. In Example 2, the theoretical drug content is about 61%, and the range in the size of the microspheres is from about 45 to about 63 microns. In Example 3, the theoretical drug content is about 65%, and the range in particle size of the microspheres is from about 45 to about 63 microns.

The microspheres of Examples 1-3 are then suspended in a suitable media for injection, in this case water. Thereafter, the microspheres are subjected to in-vitro dissolution testing. An automated dissolution test method is utilized using the USP/NF Paddle Method II. The dissolution medium is 900 ml of Tris buffer with 0.05% sodium dodecyl sulfate at pH 7.4 at 37° C with a stirring speed of about 50 RPM. The surfactant is added in order to prevent the microspheres from floating on the surface of the dissolution medium. Further information concerning these formulations is presented in Table 1 below.

TABLE 1						
Formulation	M-Sphere Size Range	Theoretical % Drug	Actual % Drug	MW of 50:50 dl-PLGA	In vitro Release	
					24 hrs	72 hrs
Ex. 1	45-90 $\mu$	62%	47%	--	28%	68%
Ex. 2	45-63 $\mu$	61%	56%	50K	52%	91%
Ex. 3	45-63 $\mu$	65%	59%	50K	22%	46%

From the results set forth in Table 1, no correlation between drug content and release rate can be readily made.

It was expected that the formulation of Example 3 would release drug faster than that of Example 1 because of a higher drug content. However, the in-vitro release for Example 3 was slower than expected. It is hypothesized that this is due to the glass transition temperature of the polymer being lowered (below about 37°C) by the high drug content. This situation may or may not be translated into in-vivo results.

#### EXAMPLES 4-9 (SPRAY-DRIED)

In Examples 4-9, the bupivacaine base and the polymer utilized in Examples 1-3 are once again dissolved in ethyl acetate, but this time the microspheres are obtained by spray-drying the solution. Example 4 utilizes a relatively high drug content, whereas Example 5 utilizes a relatively low drug content. In Examples 7-9, microspheres having a substantially similar drug content to Examples 4-5 are prepared using the solvent extraction technique utilized in Examples 1-3. Details of the formulations are presented in Table 2 below.

<u>TABLE 2</u>			
<i>Formulation</i>	Drug Content (Theoretical)	Yield	Process
Ex. 4	49%	55%	Spray-Dried
Ex. 5	29%	64%	Spray-Dried
Ex. 6	45%	--	Spray-Dried
Ex. 7	47%	62%	Solvent Extraction
Ex. 8	28%	74%	Solvent Extraction
Ex. 9	60%	60%	Solvent Extraction

With regard to Example 9, the actual percentage of bupivacaine base in the microspheres is 51%, the molecular weight of the 50:50 dl-PLGA polymer is 18,000, the microspheres were about 45-63 microns, and in-vitro dissolution

conducted as in Examples 1-3 showed that 61% of the bupivacaine was released in 22 hours.

The microspheres of Examples 6 and 9 are suspended in a suitable injection medium (e.g., water) and then subjected to in-vitro dissolution testing via the procedures set forth in Examples 1-3. The in-vitro dissolution results are determined for 22 hours.

The in-vitro dissolutions of Examples 4-5 and 7-8 are determined as per the Examples above, and compared to the dissolution of the bupivacaine free base and the bupivacaine hydrochloride salt forms. When compared to pure bupivacaine base, each of Examples 4-5 and 7-8 showed a distinct retarding effect in their dissolution profile. Furthermore, all four examples of the invention displayed a small initial burst of drug release which was more pronounced in the microspheres prepared by the spray-dried process as compared to the examples prepared by the solvent extraction process.

Scanning electron micrographs of the microspheres for the formulations prepared by the solvent extraction and by the spray-dried technique are then compared. The spray-dried process yields microspheres which are smaller than with the solvent extraction process.

#### Example 10

Local anesthesia Induced by  
Controlled Release Microspheres  
is Prolonged by Co-Administration  
of Dextran Augmenting Agent in the  
Injection Solution

Microspheres are prepared which contain 75% bupivacaine, by weight. The duration of local anesthesia induced by the bupivacaine-loaded microspheres, prepared from PLGA 65:35, with and without the co-administration of an augmenting agent, is tested in a rat sciatic nerve model for localized local anesthesia. In this procedure, groups of rats are selected that demonstrate normal

behavior in a leg withdrawal latency test at least a week prior to the experimental procedure. The latency test determines the time, in seconds, before a rat withdraws its hindpaw from a hotplate set to a safe but uncomfortable temperature (56°C).

5 Selected rats are injected with a solution containing a suspension of bupivacaine-loaded microspheres plus co-administered augmenting agent on one side and injected with a control on the contralateral side so that each rat serves as its own control. Each injection is adjacent to the sciatic nerve. The controls are bupivacaine-loaded microspheres without co-administered augmenting agent and microspheres without any bupivacaine.

10 A. Sensory Testing

As previously discussed, the degree of sensory local anesthesia is measured by determining the time or latency, in seconds, before each rat withdraws its hindpaw from a hotplate set to a safe but uncomfortable temperature. Maximum sciatic nerve sensory blockade is defined as having a latency of about 12 seconds or higher.

15 B. Motor Testing

The degree of motor blockade is measured by scoring the appearance of the affected foot for the signs of loss of motor tone. The assessment is conducted as follows using a 4-point scale based on visual observation: (1) normal appearance, (2) intact dorsiflexion of foot with an impaired ability to splay toes when elevated by the tail, (3) toes and foot remained plantar flexed with no splaying ability, and (4) loss of dorsiflexion, flexion of toes, and impairment of gait.

20 C. Experimental Protocol

25 Twenty-four rats each receive an injection of bupivacaine-loaded controlled release microspheres into the left or right side, co-administered with a dextran containing injection solution. The contralateral side receive either bupivacaine-



loaded microspheres at the same dose, or unloaded microspheres co-administered with a dextran injection solution.

Sensory hot plate latency is measured from the time of the injections until the latency declined to under 2 seconds.

5 Motor blockade is scored until the hind paws of motor blockades rats returned to a normal appearance.

The dose of bupivacaine contained in each sciatic nerve injection ranges from 5 to 450 mg/kg of rat or about 1.5 to 50 mg at each injection site.

10 The tested dextrans has a molecular weight ranging from 20 kDa through 200 kDa. The injection solution containing dextran is buffered to a pH ranging from 7.0 to 8.3.

#### D. Results

15 On the sides receiving co-administered dextran augmenting agent show a significantly longer duration of sensory block and significantly increased duration of motor block than do the sides receiving controlled-release bupivacaine-loaded microspheres without co-administered dextran. Unloaded microspheres with dextran alone produce no sensory blockade.

20 **Example 11:** Local anesthesia Induced by Controlled Release Microspheres Is Prolonged by Co-Administration of Alkalinizing Agents in The Injection Solution

25 Preparation of microspheres and testing procedures are as described above. In this experiment it is shown that co-administration of alkalinizing agents in the injection solution serve to significantly prolong the duration of local anesthesia induced by the injection of controlled release bupivacaine-loaded microspheres adjacent to rat sciatic nerve.

**A. Experimental Protocol**

Twenty-four rats each receive an injection of bupivacaine-loaded controlled release microspheres into the left or right side, adjacent to the sciatic nerve, in carbonate-buffered injection solution. The contralateral side receives either bupivacaine-loaded microspheres at the same dose at pH 7.4, or unloaded microspheres with the same injection buffer as the treatment side. The pH of the experimental injection solution ranges from pH 7.0 through pH 8.3.

**B. Results**

The degree of sensory and motor local anesthesia show a significant increase in duration proportional to the alkalinity of the carbonate-buffered injection solution, with the optimum results obtained as the pH approached 8.

**Example 12:**      **Local anesthesia Induced by Controlled Release Microspheres Was Prolonged by Co-Administration Of Agents With Diverse Pharmacological Activity**

In this example, a large number of pharmaceutical agents were tested for activity in augmenting the duration of local anesthetic activity. Bupivacaine-containing microspheres at about 75% loading, by weight, were injected perineurally into rat sciatic nerve at a dose of 150mg/kg (weight microspheres/weight rat) to dose of approximately 50 mg/nerve. For the injections, needle placement adjacent to the target nerve was optimized by intermittent electrical stimulation of the target nerve (via the injection needle) with low amplitude current to produce limb flexion. For the injections, the microspheres were suspended in a carrier vehicle suitable for injection. While any pharmaceutically acceptable carrier vehicle is acceptable, for these experiments the carrier vehicle was 1% sodium carboxymethylcellulose and 1% Tween 80 in water.

Compounds to be tested were co-injected with bupivacaine containing microspheres (i.e., mixed as additives into the carrier vehicle) in a range of

concentrations. Results are expressed as percent increase in duration relative to non-augmented durations that were obtained in the same animal model.

The duration of anesthesia was measured by the hotplate foot withdrawal method described above in Example 10 and refers to the time necessary for the animal to recover from maximal nerve latency (12 sec) to a latency of 7 seconds, approximately 50% recovery. The results are tabulated in Table 3 below as percent of control.

<b>TABLE 3</b> <b>Efficacy of Additives to LAB</b> <b>As Percent of Control Without Additive</b>			
Additive	% Additive Conc.	Duration Anesthesia As Percent of Control	Principle Pharmacological Activity of Additive
Allotetrahydrocortisone	0.05	100	Steroid, GABA receptor modulator
Allotetrahydrocortisone	0.5	117	
Alphaxalone	0.05	169	Steroid, GABA receptor modulator and anesthetic
Alphaxalone	0.5	123	
Aminopyridine (4-AP)	0.05	77	Potassium channel blocker
Aminopyridine (4-AP)	0.11	92	
Aminopyridine (4-AP)	1.09	131	
Aminopyrine	0.05	146	Analgesic
Aminopyrine	0.5	62	
Benzamil	0.05	83	Sodium channel inhibitor
Benzamil	0.5	154	
Clonidine	0.05	122	Partial $\alpha_2$ adrenergic agonist and vasoconstrictor.
Clonidine	0.5	71	

**TABLE 3**  
**Efficacy of Additives to LAB**  
**As Percent of Control Without Additive**

Colchicine	0.1	677, 1308	Microtubule inhibitor, inhibitor of glucose metabolism in leukocytes (among other properties).
Colchicine	1.0	277	
Colchicine	10	toxic	
Colchicine (Placebo)	0.1	0	
Colchicine (no LAB)	10	0	
Dehydroepiandrosterone <sup>†</sup>	0.05		Steroid, GABA receptor modulator
Dehydroepiandrosterone <sup>†</sup>	0.5		
Dextran	3	46-144	Osmotic polysaccharide
Dextran	6	Anesthesia continued past end of test period	

**TABLE 3**  
**Efficacy of Additives to LAB**  
**As Percent of Control Without Additive**

Diazepam	0.05	231	Modulates GABA receptor
Diazepam	0.5	203	
Diazoxide	0.05	138	Potassium-ATP channel agonist
Diazoxide	0.5	109	
5,5-diphenylhydantoin	0.05	145, 119	Sodium channel inhibitor
5,5-diphenylhydantoin	0.11	152	
5,5-diphenylhydantoin	1.09	138	
Minoxidil	0.05	54	Potassium channel agonist
Minoxidil	0.5	218-265	
Ouabain	0.05	154	Na,K-ATPase inhibitor
Ouabain	0.5	178	
Spantide	0.05	119	Neurokinin antagonist
Spantide	0.5	172	
Taxol	0.05	188, 138	Microtubule assembly promoter
Taxol	0.11	104	
Taxol	0.5	82	
Taxol	1.09	108	
Tetraethylammonium	0.05	95	Potassium channel blocker
Tetraethylammonium	0.5	123	
U-73, 122*	0.05	106	PLC inhibitor
U-73, 122*	0.5	115	
Valproic Acid	0.05	152	Potassium channel opener
Valproic Acid	0.5	138	
Vinblastine	0.05	158	Microtubule inhibitor
Vinblastine	0.11	37	
Vinblastine	1.09	40	

\* (1-[6-[[17-beta-3-methoxyestra-1,3,5(10)-triene-17-yl]amino]hexyl]-1-H-pyrrole-2,5-dione)

5                   **EXAMPLE 13 (EPINEPHRINE AS AUGMENTING AGENT)**

Microspheres containing bupivacaine loaded to about 75 percent by weight with bupivacaine are prepared, with and without added epinephrine, in a percent loading of about 0.05 percent, by weight, using the methods described in  
10                   EXAMPLES 1-3 or EXAMPLES 4-9, above.

Following the protocol set forth in EXAMPLE 10, above, selected rats are injected adjacent to the sciatic nerve with a solution containing a suspension of bupivacaine-loaded microspheres on the right side, and on the left side with a solution containing a suspension of bupivacaine-loaded microspheres and also  
15                   containing 0.05 percent epinephrine.

Sensory and motor testing is conducted according to sections A and B, respectively, of EXAMPLE 10, above. Using the experimental protocol of section C of EXAMPLE 10, 24 rats are tested.

On the sides receiving a combination of bupivacaine and epinephrine in controlled release microspheres, a significantly longer duration of sensory block and  
20                   significantly increased duration of motor block was obtained than with the sides receiving controlled-release bupivacaine-loaded microspheres without controlled release epinephrine.

25                   **EXAMPLE 14 (AMPHETAMINE AS AUGMENTING AGENTS)**

In experiments conducted according to EXAMPLE 13, above, amphetamine is substituted for epinephrine, with the same concentrations of each agent. On the sides receiving a combination of bupivacaine and amphetamine containing controlled release microspheres, a significantly longer duration of sensory block and  
30                   significantly increased duration of motor block was obtained than with the sides

receiving controlled-release bupivacaine-loaded microspheres without controlled release amphetamine.

**EXAMPLE 15 (EPHEDRINE AS AUGMENTING AGENT)**

5           Microspheres containing bupivacaine loaded to about 75 percent by weight with bupivacaine are prepared, in a percent loading of about 0.05 percent, by weight, using the methods described in EXAMPLES 1-3 or EXAMPLES 4-9, above. In addition, microspheres containing added epinephrine, in a percent loadings of 0.001 percent, 0.05 percent and 1 percent, without bupivacaine, are also  
10       prepared according to EXAMPLES 1-3 or EXAMPLES 4-9, above.

          Following the protocol set forth in EXAMPLE 10, above, selected rats are injected adjacent to the sciatic nerve with a solution containing a suspension of bupivacaine-loaded microspheres on the right side, and on the left side with a solution containing a suspension of bupivacaine-loaded microspheres and also  
15       containing epinephrine containing microspheres in each dose level.

          Sensory and motor testing is conducted according to sections A and B, respectively, of EXAMPLE 10, above. Using the experimental protocol of section C of EXAMPLE 10, 24 rats are tested for each of the three epinephrine dose levels by injecting epinephrine-containing microspheres (same number of microspheres per  
20       rat, adjusted for animal weight) at about the same time as the bupivacaine-containing microspheres are administered

          On the sides receiving a combination of bupivacaine microspheres and epinephrine microspheres, a significantly longer duration of sensory block and significantly increased duration of motor block was obtained than with the sides  
25       receiving controlled-release bupivacaine-loaded microspheres without controlled release epinephrine for each dose level, with the effect showing a dose-response curve according to concentration.

          As can be appreciated, a substantial range of pharmaceutical agents is capable of augmenting the duration of local anesthetic activity. In addition, these

compounds were tested as additives in the vehicle suspending the microspheres. Including an augmenting agent into the controlled release formulation itself is expected to substantially improve the prolongation of local anesthetic activity by prolonging the presence of augmenting agent at the anesthetized site.

5           The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims. Numerous publications are cited herein, the disclosures of which are incorporated herein by reference in their entireties.



**WHAT IS CLAIMED IS:**

1. A formulation for inducing sustained regional local anesthesia in a patient comprising  
a substrate comprising a local anesthetic and an effective amount of a biocompatible, biodegradable controlled release material prolonging the release of said local anesthetic from said substrate to obtain a reversible local anesthesia when implanted or injected in a patient, and  
a non-toxic, augmenting agent effective to prolong the duration of said local anesthesia for a time period longer than that obtainable from the substrate without said augmenting agent, wherein said augmenting agent is not glucocorticosteroid agent.
2. The formulation of claim 1, wherein said substrate comprises microspheres and said microspheres are suspended in a pharmaceutically acceptable medium for injection.
3. The formulation of claims 1 and 2, wherein at least a portion of said augmenting agent is incorporated in said substrate.
4. The formulation of claims 1 and 2, wherein at least a portion of said augmenting agent is in immediate release form.
5. The formulation of claim 1, wherein the biocompatible material comprises a polymer selected from the group consisting of polyanhydrides, copolymers of acid and glycolic acid, poly(lactic) acid, poly(glycolic) acid, polyesters, polyorthoesters, proteins, polysaccharides and combinations thereof, capable of degrading at least fifty percent in less than two years following implantation into the patient.
6. The formulation of claim 1 wherein the substrate is in a form selected from the group consisting of slabs, rods, beads, pellets, microparticles, microspheres, microcapsules, spheroids and pastes.
7. The formulation of claim 1, wherein the local anesthetic is incorporated into said controlled release material at a percent loading of 0.1% to 90% by weight.

8. The formulation of claim 7 wherein the local anesthetic is selected from the group consisting of bupivacaine, ropivacaine, dibucaine, etidocaine, tetracaine, lidocaine, xylocaine, mixtures thereof, and salts thereof.

9. The formulation of claim 1 wherein the augmenting agent is an effective amount of an agent selected from the group consisting of alphaxalone, allotetrahydrocortisone, aminopyrine, benzamil, clonidine, minoxidil, dehydroepiandrosterone, dextran, diazepam, diazoxide, ouabain, digoxin, spantide, taxol, tetraethylammonium, valproic acid, vincristine, a catecholamine in controlled release form, 1-[6-[[17-beta-3-methoxyestra-1,3,5(10)-triene-17-yl]amino]hexyl]-1-H-pyrrole-2,5-dione, and active derivatives, analogs and mixtures thereof.

10.. The formulation of claim 1 wherein at least part of said augmenting agent is incorporated into said substrate at a percent loading ranging from about 0.001 to about 30% by weight, preferably from about 0.005% to about 15%, by weight.

11. The formulation of claim 14 wherein the augmenting agent is effective to prolong the duration of local anesthesia from about 15% to about 1400% of the duration of local anesthesia induced by controlled release local anesthetic without the augmenting agent.

12. The formulation of claim 14 wherein the augmenting agent is a neuroactive steroid, preferably alphaxalone and/or dehydroepiandrosterone.

13. The formulation of claim 21 wherein the augmenting agent is a dextran having a molecular weight ranging from about 20 kDa to about 200 kDa and is incorporated into said substrate at a percent loading of 0.01 to 30% by weight.

14. A formulation according to claim 1 wherein the augmenting agent is an effective amount of a pharmaceutically acceptable vasoconstrictor agent in controlled release form.

15. A formulation according to claim 14 wherein the vasoconstrictor agent is selected from the group consisting of clonidine, guanfacine, guanabenz, dopa, methyldopa, ephedrine, amphetamine, methamphetamine, methylphenidate,

ethylnorepinephrine, ritalin, pemoline, epinephrine, norepinephrine, dopamine, metaraminol, phenylephrine, methoxamine, mephentermine, ephedrine, methysergide, ergotamine, ergotamine, dihydroergotamine, sumatriptan and analogs, including active metabolites, derivatives and mixtures of any of the foregoing.

16. A formulation for inducing sustained regional local anesthesia in a patient comprising

a substrate comprising a local anesthetic and an effective amount of a biocompatible, biodegradable, controlled release material prolonging the release of said local anesthetic from said substrate to obtain a reversible local anesthesia when implanted or injected in a patient, and

a non-toxic non-glucocorticoid augmenting agent effective to prolong the duration of said local anesthesia, said formulation providing an *in vitro* release of said local anesthetic of from about 10 to about 60 percent after 24 hours, from about 20 to about 80 percent release after 48 hours and from about 40 to about 100 percent release after 72 hours, said formulation providing a reversible local anesthesia at the site when administered *in vivo* of at least about 24 hours.

17. A controlled release formulation for inducing sustained regional local anesthesia at a site in a patient comprising

a local anesthetic incorporated in a controlled release formulation consisting essentially of a biocompatible material, said material degrading at least fifty percent in less than six months following implantation into a patient, wherein the local anesthetic is present in a concentration effective to achieve local anesthesia in the patient, and an effective amount of a non-glucocorticoid augmenting agent effective to prolong the duration of the local anesthesia.

18. Lyophilized particles suitable for deposit at a site in a patient in need of local anesthesia comprising

a substrate comprising a local anesthetic and an effective amount of a biocompatible, biodegradable, controlled release material prolonging the release of said local anesthetic from said substrate to obtain a reversible local anesthesia when

injected in a patient and a non-glucocorticoid augmenting agent effective to prolong the duration of said local anesthesia for a time period longer than that obtainable from the substrate without said augmenting agent, wherein said substrate is lyophilized.

19. A unit dosage form of the lyophilized particles according to claim 18 that is sterilized and is in a container comprising an amount of said lyophilized particles sufficient to induce prolonged local anesthesia in at least one patient upon suspension of said controlled release form in a solution acceptable for deposit into a patient.

20. A unit dosage form of the lyophilized particles according to claim 18 wherein an amount of said lyophilized particles sufficient to induce local anesthesia in at least one patient is sterile and provided in a sealed container ready for use.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/10439

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>				
IPC(6) : A61K 9/14, 31/715, 31/56, 31/505, 31/24, 31/19 US CL : 424/484, 487, 489; 514/58, 179, 256, 535, 557 According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b>				
Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/484, 487, 489; 514/58, 179, 256, 535, 557				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched none				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS, Cas-Online				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	WO, A1, 94/05265 (CHILDREN'S MEDICAL CENTER CORPORATION) 17 March 1994, see the entire document.	1-20		
Y	M. WINDHOLZ et al., "THE MERCK INDEX", published 1983 by MERCK & CO., Inc (N.J.), see page 37, abstract no. 225.	1-20		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.				
<table border="0"> <tr> <td> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>			
Date of the actual completion of the international search 16 AUGUST 1996		Date of mailing of the international search report <b>03 SEP 1996</b>		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer KEVIN WEDDINGTON Telephone No. (703) 308-1235		